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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/535,951	03/27/2000	Alan D. Schreiber	555-56	4293

7590 12/18/2002

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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	12

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/535,951	SCHREIBER, ALAN D.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 27, 2002 has been entered.

The amendments of claim 8 filed July 29, 2002 have been entered.

Claim Rejections – 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 -12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "progestational agent that has an effect on the function of the sex organs of said mammal **less than** that of medroxyprogesterone" in claim 8, line 4 renders the claims indefinite. It is unclear what progestational agents are encompassed by the claim. Further, the nature of "function" on the sex organs encompassed by the claims is unclear. Moreover, as discussed in the advisory action mailed , the effect of medroxyprogesterone on the function of the sex organ is dose-dependent. For example, a 20mg of medroxyprogesterone would produce a stronger effect on the

function of sex organ than a 5mg of medroxyprogesterone. The instant claim does not recite the dose of medroxyprogesterone and therefore, fail to make clear what effect of medroxyprogesterone is being compared with the instant progestational agent.

Without knowing exactly what effects and the degree on the function of the sex organs may encompassed by the claim, one of ordinary skill in the art would not know what progestational agents are considered to be encompassed by the claims as being lesser in such effect than medroxyprogesterone.

The expression "non-steroidal compounds that inhibits macrophages or macrophage function" recited in claims 10 – 12 renders the claims indefinite as to the non-steroidal compounds, other than the compounds listed in the instant specification page 4, line 17- page 5, line 12, are encompassed by the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aristoff et al. (WO90/15816) and Blei et al. (Journal of Cellular Physiology, 1993; 155: 568-578) in view of Kuzuya et al. (J Cell Physiol, 1995; 164(3):658-667), references of record.

Aristoff et al. teaches a method of inhibiting angiogenesis disorders, broadly, including atherosclerosis using angiostatic steroid compounds, broadly, including 17-hydroxyprogesterone (see particular page 3, line 22 and page7, line 30; claim 8).

Blei et al. teaches series of tests are performed to determine the mechanism of action for several angiostatic steroids, including 17-hydroxyprogesterone, in inhibiting angiogenesis (See abstract). Blei et al. teaches 17-hydroxyprogesterone is effective in suppressing the plasminogen activator level increase, which is in response to the addition of angiogenetic factor: basic fibroblast growth factor (bFGF), by 27% (See page 570, col. 2, last paragraph).

The references do not expressly teach the use of 17-hydroxyprogesterone in a method to reduce atherosclerotic plaque.

Kuzuya et al. teaches that the development of atherosclerotic plaque is associated with neovascularization (angiogenesis) in the thickened intima and media of vascular walls (See the abstract). Kuzuya et al. also teaches that the progression of atherosclerotic plaque may be contributed through the secretion of angiogenic factor by the smooth muscle cells (See particularly the abstract). Kuzuya et al. also teaches that the extent of neovascularization is correlated with the severity of atherosclerosis (See page 658, col. 1, second paragraph). Kuzuya et al. also teaches that the regression of an atherosclerotic lesion by regression of neovascularization (See page 658, col. 1, second paragraph).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to use 17-hydroxyprogesterone in a method to reduce atherosclerotic plaque.

One of ordinary skill in the art would have been motivated to use 17-hydroxyprogesterone in a method to reduce atherosclerotic plaque because any known angiostatic steroid compound including 17-hydroxyprogesterone, would have been reasonably expected to be useful in a method of inhibiting angiogenesis and reducing atherosclerotic plaque thereby since angiogenesis is known to be contributive factor in the progression of atherosclerotic plaque.

Claims 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cincotta (US Patent 5,565,454) in view of de Gruijter et al. (Metabolism, 1991; 40(11):1119-1121), reference of record.

Cincotta et al. teaches a method of in treating atherosclerosis using prolactin enhancer and/or prolactin inhibitors including haloperidol (see particular Col. 1, line 32 - Col.2, line 15; also Col.2, line 25 – 34; also Col.6, line 5-9). Cincotta et al. also teaches that prolactin enhancer could reduce the plasma triglyceride and cholesterol level (See col. 2, line 25-36). Cincotta et al. teaches that platelets and monocytes adhesion to the endothelium connective tissues may lead to restenosis (See col. 1, line 48 - col.2, line 15).

Cincotta et al. does not expressly teach the use of haloperidol specifically in a method of reducing atherosclerotic plaque.

de Gruijter et al. teaches Hypercholesterolemia or combined Hypercholesterolemia-hypertriglyceridemia increase the adhesion of monocytes to the endothelium of the vessel wall that result in atherosclerotic plaque (See abstract and page 1121, col. 1).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to use haloperidol in a method to reduce atherosclerotic plaque.

One of ordinary skill in the art would have been motivated to use haloperidol in a method to reduce atherosclerotic plaque because any known prolactin modulator compounds, including haloperidol, would have been reasonably expected to be useful in a method of reducing the platelets and monocytes adhesion to the endothelium or subendothelial connective tissue and reducing the plasma cholesterol and triglyceride level in patients. Elevated cholesterol and triglyceride level and increased adhesion of moncytes to the endothelium of bloods vessel walls are known to increase the formation of atherosclerotic plaque. Therefore, reducing the plasma triglyceride and cholesterol level and adhesion of platelets and moncytes to the endothelium of blood vessel walls by a known prolactin enhancer such as haloperidol would have been reasonably expected to reduce atherosclerotic plaque based on the cited prior art, absent evidence to the contrary.

Response to Arguments

Applicant's rebuttal arguments filed July 29, 2002 averring Aristoff et al.'s teaching of a combination of suramin-type compound with 17-hydroxyprogesterone for

inhibiting angiogenesis and therefore, no motivation to employ 17-hydroxyprogesterone alone to inhibit the same, have been considered, but are not found persuasive. 17-hydroxyprogesterone is known in the art as angiostatic steroids (See Blei et al.). Therefore, administering 17-hydroxyprogesterone to reduce angiogenesis and atherosclerosis thereby would be reasonably expected to be effective.

Applicant's rebuttal arguments filed July 29, 2002 averring the cited prior art fail to teach that neovascularization causes atherosclerotic plaque and therefore, no motivation is provided by the cited prior art to administer 17-hydroxyprogesterone to reduce atherosclerotic plaque, have been considered but are not found persuasive. Kuzuya et al. clearly provides a motivation to inhibit angiogenesis (neovascularization) in order to reduce the atherosclerotic lesion (plaque) (See particularly 658, col. 1, second paragraph).

Applicant's rebuttal arguments filed July 29, 2002 averring Cincotta et al. and e Gruiter et al. not teaching or suggesting the instant invention via the newly discovered mechanism have been considered, but are not found persuasive. de Gruijter et al. teaches Hypercholesterolemia or combined Hypercholesterolemia-hypertriglyceridemia could increase the adhesion of monocytes to the endothelium of the vessel wall that result in atherosclerotic plaque (See abstract). Therefore, by lowering the serum triglyceride and cholesterol level, one of ordinary skill in the art would reasonably expect the atherosclerotic plaque load to be reduced. Since haloperidol is a known prolactin enhancer, which is known to be useful in reducing triglycerides and cholesterol level, employing haloperidol, a known prolactin enhancer, to lower serum triglyceride level

and reduce atherosclerotic plaque thereby would be reasonably expected to be useful, absent evidence to the contrary.

Applicant's data in example 1 in the instant specification, which is the only example related to the claimed method of reducing atherosclerotic plaque load, in the specification has been considered but is not found persuasive because the example merely demonstrates the effectiveness of progesterone and haloperidol in the method of reducing atherosclerotic plaque. There is no comparative data present. This is seen to be an expected effect based on the cited prior art. No convincing and clear unexpected result is seen. Moreover, the experiment, while only testing haloperidol, is not reasonably commensurate with the scope of the herein claimed subject matters. The claims are drawn to all non-steroidal compounds that inhibits macrophages or macrophage function.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
December 9, 2002

SREENI PADMANABHAN
PRIMARY EXAMINER
12/13/02